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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/040,518	03/17/98	KARATZAS C	06632/011001

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/040,518	Karatzas et al.
Examiner	**Group Art Unit**
Anne-Marie Baker, Ph.D.	1632

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-21* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-21* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 and 9*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-21 are pending in the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 2, 3, 5, and 6 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 2 is drawn to a mammalian embryo which would encompass a human embryo which is non-statutory subject matter. Claims 3, 5, and 6 are drawn to transgenic animals which would encompass human beings which is non-statutory subject matter. See MPEP 2105. Inclusion of the phrase "non-human" would be remedial.

Claim 2 is rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The claimed invention is not supported by either a specific asserted utility or a well-established utility.

The claim is drawn to a mammalian embryo whose nucleus comprises a nucleic acid molecule encoding a biofilament operably linked to a promoter and leader sequence that direct expression of the biofilament in milk-producing cells or urine-producing cells.

Neither the specification as filed nor any art of record discloses or suggests any specific use for the claimed mammalian embryo. As the embryo does not secrete milk or excrete urine, the embryo cannot be used to produce biofilaments.

No specific asserted utility or well-established utility is disclosed for the mammalian embryo harboring the recited construct.

Note that, because the claimed invention is not supported by a specific asserted utility as set forth above, credibility cannot be assessed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 2 is also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 3-6 are rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The phenotype of the transgenic animal critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

Claims 3-6 do not recite any particular phenotype for the claimed animals. However, the phenotype exhibited by the transgenic animals, i.e. the expression and secretion of the biofilament, is required to enable the use of the animals as a source for the isolation of biofilaments. The specification does not teach how to use animals lacking this phenotype. This rejection could be overcome by amending the claims to recite the phenotype of the claimed animals.

Claims 1 and 3-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 7-12 are directed to a nucleic acid molecule encoding a biofilament, wherein said nucleic acid molecule is operably linked to a promoter and a leader sequence that directs expression and secretion of the biofilament from milk-producing cells or urine-producing cells. Claims 3-6 are directed to transgenic animals that express a biofilament in milk-producing cells or urine-producing cells. Claims 13-21 are directed to a method for producing a biofilament *in vitro* or *in vivo*.

The specification fails to provide an enabling disclosure for the preparation of a transgenic animal of the type claimed because the phenotype of a transgenic animal cannot be predicted. Furthermore, the specification fails to provide an enabling disclosure for the preparation of any and all species of transgenic animals of the type claimed. The specification does not teach how to obtain sufficient amounts of biofilaments from the claimed animals. The specification only teaches the anticipated expression of the transgene, but the specification does not offer adequate guidance to teach one skilled in the art how to produce a transgenic animal that expresses a biofilament in milk or urine to a level sufficient to allow purification of the biofilament from the biological fluid. The mere capability to perform gene transfer in any given species is not enabling for the claimed transgenic animals because the desired phenotype (in this case, the expression of a biofilament in milk or urine at a level sufficient to permit isolation and purification of the biofilament) cannot be predictably achieved simply by introducing transgene constructs of the type recited in the claims. While gene transfer techniques are well-developed for a number of species, especially the mouse, methods for achieving the desired level of transgene expression in appropriate tissues are less well-established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably

by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse will not necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, there are inherent physiological differences between mice, goats, cows, sheep, etc. that can affect the phenotype in an unpredictable manner. In the absence of specific guidance, the existence of any phenotypic alteration resulting from the introduction of a nucleic acid construct comprising a biofilament gene operably linked to a milk-specific or urine-specific promoter in any species of animal is highly unpredictable. Given the lack of working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to make and use the claimed transgenic animals.

The specification fails to provide an enabling disclosure for the claimed nucleic acid constructs because the constructs are not enabled for the intended use for the reasons discussed herein above. The

claims recite an intended use, wherein the leader sequence "enables secretion of said biofilament by said milk-producing cells or said urine-producing cells, into milk or urine, respectively, of a mammal." However, for the reasons discussed above the specification is not enabling for the use of the nucleic acid construct to produce transgenic animals that express a biofilament in the milk or urine.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided in the disclosure to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover any transgenic animal harboring any construct of the type recited in the claims, but the specification does not enable such animals nor the use of such animals in the claimed methods. In the absence of disclosure of a transgenic animal exhibiting the appropriate phenotype, undue experimentation would have been required to make and use the claimed animals.

With regard to Claims 13 and 15-21, the specification fails to provide an enabling disclosure for the preparation of any and all species of transgenic animals by the method recited in the claims because the guidance offered in the specification is limited to the preparation of mice and no teachings or guidance are offered in regard to how one would have prepared any other type of animal using the claimed method. The specification teaches on page 7, lines 4-7 that an "embryonal cell" is a cell that is capable of being a progenitor to all the somatic and germ-line cells of an organism. Exemplary embryonal cells are embryonic stem cells (ES cells) and fertilized oocytes. However, the claimed method involves transfecting an "embryonal cell," but neither the prior art nor the instant specification teach how to transfect fertilized oocytes. The prior art does, however, teach how to transfect ES cells. But ES cell technology is limited to the

mouse. As ES cell technology must be available to carry out the claimed method, and the only species in which such technology was known was the mouse, and the artisan did not accept that it was possible to have prepared ES cells in other species (see e.g., Bradley et al., paragraph bridging pages 537-538), the claimed methodology must be limited to the mouse. Campbell and Wilmut (1997) acknowledge reports of ES-like cell lines in a number of species, but emphasize that as yet ther are no reports of any cell lines which contribute to the germ line in any species other than the mouse (p. 65). Since ES cell technology was required to practice the claimed methods, in the absence of such technology available in other species, one skilled in the art would have been required to exercise undue experimentation in the practice of the claimed methods in species other than mice.

With regard to Claims 13-21, the specification fails to provide an enabling disclosure for the method for producing a biofilament *in vivo* in a transgenic animal because the claims recite "secretion of said biofilament from a cell derived from said transfected embryonal cell," but the teachings in the specification are limited to expressing the biofilament in a milk-producing cell or urine producing cell. The specification does not teach appropriate promoters or leader sequences for expressing a biofilament in other types of cells/tissues. Undue experimentation would have been required for one skilled in the art to practice the claimed method wherein the biofilament is expressed in any type of cell. Furthermore, for the reasons discussed above, undue experimentation would have been required to practice the claimed method wherein the biofilament is expressed in a milk-producing or urine-producing cell.

Claims 2-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the

inventors, at the time the application was filed, had possession of the claimed invention. Applicants are referred to the revised interim guidelines on written description published December 21, 1999 in the Federal Register at Volume 64, Number 244, pp. 71427-71440 (also available at www.uspto.gov).

The claims are directed to a mammalian embryo and transgenic animals that express a biofilament in milk or urine. However, the specification does not disclose any animal of the type claimed. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In this case, since phenotype cannot be predicted for a transgenic animal for the reasons discussed above and no working examples describe a transgenic animal of the type claimed, no transgenic animals have been described by their complete structure. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In this case, since phenotype cannot be predicted from the transgene introduced, no identifying characteristics are provided for transgenic rodents, goats, cows, or any other animal. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of a transgenic animal of the type claimed at the time the application was filed. Thus, it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-6 and 13-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in its recitation of "whose nucleus" because the claim refers to the nucleus of an embryo and an embryo does not have a nucleus. Only a cell has a nucleus.

Claims 3 and 4 are indefinite in its recitation of "[a] female mammal in which the genome of the mammary tissue of said female comprises the nucleic acid molecule of claim 1" because it is unclear if only the genome of mammary tissue cells comprise the transgene or if the genome of every cell of the mammal comprises the transgene. The specification is limited to the generation of transgenic animals. Transgenic animals carry a transgene in the genome of all somatic and germ cells. The specification does not teach genetically modifying mammary tissue only.

Claims 5 and 6 are indefinite because Claim 5 is directed to "[a]n animal" but said animal comprises the nucleic acid molecule of claim 1 and claim 1 recites that the leader sequence "enables secretion of said biofilament by said milk-producing cells or said urine-producing cells, into milk or urine, respectively, of a mammal." Thus, the nucleic acid of claim 1 is limited to an intended use for expression in a mammal, but claim 5 broadens the scope to include the use of the nucleic acid in any animal.

Claims 13 and 15-21 are indefinite in the recitation of "an embryonal cell transfected with a biofilament-encoding nucleic acid molecule" because the specification teaches that a fertilized oocyte constitutes "an embryonal cell," but no methodology exists for transfecting a fertilized oocyte. The specification only teaches microinjection of fertilized oocytes. Only embryonic stem cells can be transfected.

Claim 14 is indefinite because the arrangement of elements is not specified. The claim does not indicate that the promoter is operably linked to the nucleic acid sequence encoding the biofilament. Claims 15-21 are indefinite in so far as they depend from Claim 14.

Claims 14-21 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the expression and secretion of the biofilament by the transfected cell.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Baker whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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